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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,245	CHEN ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/03/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4,7 and 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8-12 and 20-25* is/are rejected.

7)☒ Claim(s) *1,2 12 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/4/04; 11/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner handling this application has changed and is now Stephen Kapushoc in Art Unit 1634. Future correspondence regarding this application should be addressed to the above-mentioned Examiner.

Claims 1-25 are pending.

Claims 4, 7, and 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claim 4 is drawn to a non-elected drug; claim 7 is crawn to a non-elected drug and non-elected allele; Claims 13-19 are drawn to a non-elected invention.

Claims 1-3, 5, 6, 8-12, and 20-25 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of the invention of Group I in the reply filed on 4/3/2006 is acknowledged. The traversal is on the ground(s) that Groups I and III can be searched and examined without a serious burden on the Examiner. The restriction requirement between groups I and III is withdrawn. Claim 20 (of the previously identified Group III) has been considered in so far as it requires the elected allele HLA-B*1502. Claim 21 has also been considered.

Applicant has further elected with traverse the allele HLA-B*1502, the drug carbamazepine, and the equivalent marker Cw*0801. The traversal is on the grounds that different HLA-B alleles are alleles of the same locus and share structural similarity. Applicant further cites MPEP 803.04, which indicates that up to ten nucleotide sequences may be examined in a single application. This is not found persuasive, as the Examiner maintains that the different alleles are in fact unique structures, requiring separate searches, where a reference against one allele would not necessarily be a

reference against any other allele. Additionally, since the writing of MEPE 803.04, the databases that are required to be searched for the examination of any biological sequence have grown tremendously, and Technology Center 1600 no longer routinely searches a multiplicity of distinct and independent sequences for any application.

The requirement is still deemed proper and is therefore made FINAL.

In Applicant's Response to Restriction filled 4/3/06, Applicants note that claims 1 and 5-12 have been considered linking claims. The restriction requirement resulted in the election of a particular single HLA-B allele (1502), a particular single drug (carabazepine), and a single particular equivalent genetic marker (Cw*0801). Claims that are generic have been examined as such, for example claim 1 is drawn to any drug, and claim 11 is drawn to any equivalent genetic marker. Claims that recite specific HLA-B alleles, drugs, and equivalent genetic markers have been examined insofar as they require the elected entities; for example claim 1 (and dependent claims) has been examined only insofar as it requires the elected HLA-B*1502, and claims 4 and 7 have been withdrawn as they specifically require only non-elected drugs and/or HLA-B alleles. Furthermore, upon a finding of allowance of an examined claim, the requirement for restriction will be withdrawn only for claims that include all of the limitations of the allowable claim.

Claim Objections

2. Claims 1, 2, 12 and 20 are objected to as specifically reciting non-elected subject matter. The Requirement for Restriction set forth on 03/02/2006 resulted in the election of claims as pertaining to HLA-B*1502, carbamazepine, and Cw*0801. The claims specifically recite non-elected alleles (HLA-B* 5801 and 4601), drugs (allopurinol, phenytoin, sulfasalazine, amoxicillin, ibuprofen, and ketoprofen), and equivalent genetic markers (HLA-DRB1*1202, CW*0806, A*1101, MICA*019, and Cw*0302). Prior to allowance, non-elected subject matter will be required to be deleted from the claim.

Claim Rejections - 35 USC § 112 1st Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 5, 6, 8-12 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for assessing the risk of a human Taiwanese patient for developing Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) in response to carbamazepine (CBZ) comprising determining the presence of an HLA-B*1502 allele wherein presence of the allele is indicative of an increased risk for SJS/TEN, does not reasonably provide enablement for assessing the risk of any other adverse reactions in response to any other drugs in any other human population or any non-human populations using any equivalent genetic marker. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to a method for assessing in a patient the risk of an adverse drug reaction in response to a drug by determining the presence of the HLA-B*1502, wherein the presence of the allele is indicative of a risk for an adverse reaction.

The claims encompass assessing risk in any patient, from any population, and encompass non-human organisms.

Claims 1, 5, and 8-12 encompass adverse drug reaction in response to any drug.

Claims 1-3 and 8-12 encompass any adverse drug reaction.

Claim 11 encompasses the use of any equivalent genetic marker.

The nature of the invention requires knowledge of a relationship between HLA-B*1502 or an equivalent genetic marker and the risk of an individual to develop an adverse reaction in response to a drug.

Direction provided by the specification and working example

The specification of the instant application teaches an analysis of HLA-B allele genotype and the development of adverse drug reaction.

The specification teaches that there are various types of adverse drug reactions, and broadly defines 'adverse drug reaction' as an undesired or unintended effect of a drug (p.8, ln.1). The specification teaches that drug eruptions may be mild to moderate

in nature (macuolpapular rash, erythema mulitforme, urticaria, fixed drug eruption) or more severe (SJS, TEN) (p.4 lns.10-17).

The specification teaches that there is evidence that adverse drug reactions involve MHC-restricted presentation of drug or drug metabolites.

The specification provides an example of a case:control analysis of HLA-B genotypes and adverse drug reactions in a Taiwanese population. The specification teaches that the 'cases' were 238 individuals with ADRs, wherein 112 patients were diagnosed with SJS/TEN adverse drug reactions (defining this adverse drug reactions as: SJS is skin detachment of less than 10% of body-surface area; overlap SJS-TEN as 10-30%; TEN as greater than 30%; where SJS, overlap SJS-TEN, and TEN are collectively referred to as SJS/TEN (p. 28, lns 6-15), and 126 individuals had milder reactions to various drugs (p.30 – Example 1). Of the 112 SJS/TEN cases, 42 had carbamazepine-induced SJS/TEN (p.28 ln.6). Controls for the analysis provided in the example were 73 carbamazepine-tolerant patients, and 94 non-patients form the general population (p.28 lns.16-21).

The specification teaches the genotyping of subjects' HLA alleles using PCR amplification with sequence specific oligonucleotides and hybridization of the amplification product to a lineblot (p.28 lns.24-30).

The specification provides an analysis of HLA alleles present in patients with carbamazepine –induced SJS/TEN as compared to patients with milder reactions, the general population, and carbamazepine-tolerant patients (Table 1; p.30 ln.29 – p.31 ln.16). The specification teaches that HLA*B-1502 was detected in 42 of 42 SJS/TEN

patients who received carbamazepine, but found only in 3 of 73 carbamazepine tolerant patients, 9 of 142 patients with mild adverse reactions, and 5 of 94 general population subjects. The results indicate that the HLA*B-1502 allele is related to carbamazepine – induced SJS/TEN in a statistically significant fashion (Table 1).

The specification does not provide any analysis of any non-human subjects, or any analysis of a non-Taiwanese population.

The specification does not teach that the HLA-B*1502 allele is associated, in a statistically significant fashion, with any adverse reactions other than SJS/TEN, or with reactions to drugs other than carbamazepine.

The specification teaches that 38 of the 42 carbamazepine-induced SJS/TEN patients also had the HLA-Cw*0801 allele. The specification does not provide any statistical analysis of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of linkage between HLA-B*1502 and HLA-Cw*0801.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to identification of a particular HLA-B allele is well developed, and the level of skill in the art of identification of an adverse drug reaction is high, the level of unpredictability with regard to the association of a particular HLA-B allele with an adverse drug reaction is even higher as evidenced by the prior art, post-filing art, and the specification of the instant application.

The specification teaches only the analysis of a Taiwanese population. It is unpredictable as to whether or not HLA-B*1502 would be indicative of risk of an adverse drug reaction in another population. The post filing art of Hung et al (2005) teaches an

analysis of HLA-B genotyping to detect carbamazepine-induced SJS. The reference teaches that alleles may be present in different frequencies in different populations, and that it is more likely to find a positive result when a study is conducted in a population with a high frequency of the allele (p.233, left col., lns.8-13). Additionally, the reference teaches that as study results can vary between study populations, it remains to be seen to what extent the association between HLA-B*1502 and CBZ-induced SJS/TEN applies to other populations (p.233, right col., lns. 11-16). Furthermore, the post filing art of Lonjou et al (2005) indicates that HLA-B*1502 is not a useful prediction marker of CBZ related SJS in the European population (p.3, left col., second paragraph).

While the claims encompass risk assessment in any organism, the specification teaches only the analysis of human subjects. It is unpredictable as to whether or not an allele similar to the human HLA-B*1502 found in another organism would be indicative of risk of an adverse drug reaction. Such unpredictability is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if alleles comprising sequences homologous to the HLA-B*1502 allele of the claims were identified in other animals, one would have to perform a large amount of experimentation to determine whether or not these genes would be useful in assessing risk of an adverse drug reaction.

The instant specification teaches the unpredictability in using HLA-B*1502 to assess drug reactions other than SJS/TEN induced by carabamazepine. The specification teaches, for example, that HLA-B*1502 was not detected in 16 patients

suffering from milder cutaneous reactions to carbamazepine (Table 2; p.31 lns.11-13). Additionally, a drug information sheet for carbamazepine (Carbamazepine, 2006) indicates that there is a wide variety of side effects (which are adverse drug reactions) related to carbamazepine (p.2 – Side effects) for which there is no data presented in the specification.

And while the specification indicates that the HLA-B*1502 allele was found in 17 of 53 SJS/TEN patients who received drugs other that carbamazepine, the specification presents no measure of the statistical significance of these results. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a p-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion. Additionally, the prior art of Leeder (1998) (as cited in the IDS) teaches that the mechanism of drug hypersensitivity is based on the production of reactive metabolites from the particular drug of interest (Fig 1; p.S9, left col., "Hapten Hypothesis"). The reference teaches that different drugs create different metabolites (p.S10 – Bioactivation of PHT and CBZ to reactive intermediates). Thus it is unpredictable as to whether or not HLA-B*1502 can be used in assessing risk of an adverse reaction to a drug other than carbamazepine.

It is unpredictable as to whether or not the presence of any 'equivalent genetic marker' is useful for determining the presence of the HLA-B*1502 allele or for the assessment of risk of drug adverse reaction. While the specification teaches that 38 of

42 carbamazepine-induced SJS/TEN patients had an HLA-Cw*0801 allele, there is no statistical analysis of the significance of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of the linkage of HLA-B*1502 with HLA-Cw*0801. Regarding the linkage of HLA-B*1502 with HLA-Cw*0801, Deng et al (2001) teaches that the traditional criteria are that a Logarithm-of -Odds (LOD) score of > 3.0 is taken as evidence for a significant linkage, a LOD score < -2.0 is taken as evidence against linkage, and a LOD score between -2.0 and 3.0 is not conclusive concerning linkage and exclusion for the genomic region under test (p.314, first full paragraph).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to use the inventions in the full scope of the claims. One would have to perform case:control studies to establish that HLA-B*1502 is associated in a statistically significant fashion with any different adverse reaction in a patient in response to any different drug. One would also have to establish that any associations are applicable to any different patient population of interest, including non-human organisms.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the paucity of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope in which it is claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 20, 21, 23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Trachtenberg (US Patent 5,550,039, Aug. 27, 1996).

Trachtenberg teaches methods for the analysis of HLA-B genotypes using PCR amplification (col.2 lns.37-59) and hybridization of the amplified product to a set of sequence –specific oligonucleotide probes (col.12 lns.38-42).

Regarding claims 20 and 21, Trachtenberg teaches a method comprising the same step as required by the claim. The reference teaches determining the presence of HLA-B alleles in a sample (col. 16 – Example 2). The data presented indicates that the presence of several different HLA-B alleles is determined, including HLA-B*1502 and HLA-B*5801 (Table 7).

Regarding claim 23, Trachtenberg teaches using sequence-specific oligonucleotides to determine HLA-B alleles (col.17 lns.4-6), which are oligonucleotides that specifically hybridize with the nucleic acid coding for the allele.

Regarding claim 25, Trachtenberg teaches the use of RNA (col.11 lns.12-17).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trachtenberg (US Patent 5,550,039, Aug. 27, 1996) in view of Yates et al (1997) as cited in the IDS.

Trachtenberg teaches methods for the analysis of HLA-B genotypes using PCR amplification (col.2 lns.37-59) and hybridization of the amplified product to a set of sequence –specific oligonucleotide probes (col.12 lns.38-42). The data presented indicates that the presence of several different HLA-B alleles is determined, including HLA-B*1502 and HLA-B*5801 (Table 7).

Trachtenberg does not teach determining the presence of the genetic factor thiopurine methyltransferase, or specifically teach analysis of DNA prepared from peripheral blood.

Regarding claims 22 and 24, Yates et al teaches the analysis of thiopurine S-methyltransferase (TPMT) by PCR analysis of the TPMT gene. The reference teaches determining the presence of the genetic factor by analysis of various nucleotide mutations (p.610 – Detection of TPMT mutations by polymerase chain reaction). Relevant to claim 24, Yates et al teaches using nucleic acids prepared from peripheral blood samples (p.609 – Methods, human patients and determination of phenotypes).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the HLA-B allele determination methods of Trachtenberg so as to have included the TMPT analysis of Yates et al. One would have been motivated to do so because Yates et al teaches the relevance of TPMT analysis applied to organ transplant recipients (p.609, left col., lns.1-6), and Trachtenberg teaches that HLA-B genotyping can be used for tissue typing (col.1 lns.38-44). It would have also been obvious to use the nucleic acids prepared from peripheral blood (as taught by Yates et al) in the HLA-B determination methods of Trachtenberg. One would have been motivated to use nucleic acids from peripheral blood because Yates et al teaches successful PCR analysis of nucleic acids from such samples (p.611 – Results).

Thus, in view of the prior art, the claimed invention is obvious.

Conclusion

9. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER
5/15/02